REMARKS

Favorable consideration of this application is respectfully requested in view of the above amendment and the following remarks.

Status

Claims 1-11, 13-16, 20 and 21 are pending in the application. All of the pending claims have been rejected. Claims 1, 4, 5, and 21 have been amended. Claim 20 has been cancelled without prejudice. It is submitted that no new matter has been added.

Support for the recitation of the phrase " the progestogenic compound being dissolved in a core of a thermoplastic polyethylene vinylacetate copolymer at a concentration below the saturation level at 25°C" can be found throughout the specification and examples as filed, in particular in paragraph [0101] wherein Applicants state that:

> [a]s illustrated by Table III and FIG. 1, examples 2-14 show that with drug delivery systems according to the invention, which have a concentration below saturation level at 25°C, a similar and sufficient release profile of etonogestrel for use in contraception and/or HRT is still obtained.

Support for the recitation of the limitation recited in the wherein clause added to claims 1, 4 and 5 can be found throughout the specification as filed, in particular in paragraph [0023] of US2007/0141102 wherein Applicants state that:

> [t]he improved drug delivery system is physically stable under room temperature conditions (about 25°C) and thus does not need special storage and transportation conditions at a temperature below room temperature.

The Office Action indicates that "[r]ejections/objections not reiterated from previous Office Actions" are withdrawn, and that the outstanding rejections are either reiterated or newly applied and constitute the complete set of objections and rejections being applied to the instant application.

The Instant Invention

The instant invention provides an improved drug delivery system (DDS) that is physically stable under room temperature storage conditions (about 25° C) consisting of one or more compartments consisting of two layers (i.e., a core and a skin) of thermoplastic polyethylene vinylacetate copolymer. The core layer of the disclosed devices comprises a progestogenic and an estrogenic compound in sufficient amounts to achieve release rates that adequate for use in contraception or hormone replacement therapy protocols.

The progestogenic compound is dissolved in the polyethylene vinylacetate copolymer up to a concentration below the saturation level at 25° C. The design of the improved DDS of the invention confers physical stability at room temperature and avoids the possibility of crystallization of the progestogen on the exterior surface of the DDS which can result in uncontrolled release rates and cause a high burst release *in vivo*.

Claim Objections

Claim 20 is objected to for the following informality: recitation of the phrase "when stored *on* or above room temperature." Claim 20 has been cancelled, which renders this objection moot. Withdrawal of the objection to claim 20 is requested.

Claim Rejections

Rejection of Claim 21 Under 35 USC § 112, Second Paragraph

Claim 21 is rejected under 35 USC 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim that subject matter which applicants regard as the invention. The Office Action alleges that the phrase "for at least approximately 21 days" is indefinite because it is unclear what ranges are encompassed by the phrase. More specifically, the Office Action alleges that the phrase "[a]t least 21 days" is a minimum that encompasses all values at or above 21 days, whereas "approximately 21 days" encompasses values both above and below 21 days. Claim 21 has been amended by deleting the phrase “at least”.

The amendment of Claim 21 renders this rejection moot. Withdrawal of the rejection of claim 21 under 35 USC § 112, second paragraph is requested.

Rejection of Claims 1-11, 13-16 and 20-21 Under 35 USC §103(a)

Claims 1-11, 13-16 and 20-21 are rejected under 35 USC §103(a) as being unpatentable over EP 0876815 (referred to herein as EP '815). The Office Action indicates in relevant part that:

> EP '815 discloses a drug delivery system comprising at least one compartment comprising (i) a thermoplastic polymer core containing a mixture of progestogenic and estrogenic compounds and (ii) a thermoplastic polymer skin wherein the thermoplastic polymer skin is permeable to the progestogenic and estrogenic compounds (abstract; page 2, line 50 to page 3, line 12; Examples 1-5) (Office Action, page 4).
>
> The progestogenic compound is dissolved in the core polymer in a relatively low degree of supersaturation, preferably being about 1 to about 6 times of the amount of weight necessary for obtaining the saturation concentration of said progestogenic steroid in said core polymer at 25° C (page 2, lines 54 to page 3, line 4; claim 4). EP '815 discloses that an essential element of the invention is for the progestogenic steroid dissolved in the core material to be present in a relatively low degrees of supersaturation and EP '815 further discloses the importance of keeping the steroid dissolved in a low concentration to improve the shelf life of the product (page 4, lines 6-24; Reference Example) (Office Action, page 5).
>
> EP '815 does not explicitly state that the mixture of a core granulate is a homogenous mixture, but the homogeneity of this mixture is inherent in the disclosed invention. This inherency is supported by the need to keep the progestogenic and estrogenic compounds dissolved in the polyethylene vinylacetate copolymer (page 3, lines 26-27) (Office Action, pages 5-6).
>
> Although EP '815 discloses keeping the progestogenic steroid in a relatively low degree of supersaturation and further discloses keeping the compound in low concentration improves the shelf life of the product, EP '815 fails to teach the range "up to a concentration below the saturation level at 25° C as required by the instant claims (Office Action, page 6).
>
> Regarding instant claim 15, the disclosed kit ony requires the presence of the instant drug delivery system. All the recited elements of the kit (i.e., the drug delivery system according to instant claim 1) are rendered obvious by EP '815 (Office Action, page 7).

> Regarding instant claim 16, the disclosed combination preparation only requires the presence of the drug delivery system according to instant claim 1. All of the recited elements of the kit are rendered obvious by EP '815 (Office Action, pages 7-8).

Based on the above-listed observations, the Office Action concludes that "[i]t would have been obvious to one of ordinary skill in the art at the time the instant invention was made to find progestogenic steroid concentrations within the range of "up to a concentration below the saturation level at 25° C because the range taught by EP '815 touches, if not overlaps with, this range (Office Action, page 6). The Office Action further indicates that "EP '815 teaches embodiments wherein the concentration of the progestogenic compound is about one times the saturation level at 25° C (claim 4), and further teaches the importance of keeping the compound dissolved in a low concentration to improve the shelf life, … the reference provides sufficient guidance to the ordinary artisan to optimize the progestogenic steroid concentration range to find values just below the saturation level at 25° C, i.e. values "up to a concentration below the saturation level at 25° C. This reasoning is supported by citing to In re Aller and MPEP §2144.05 for the premise that "[w]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation."

With regard to claims 7 (directed to the release profile of etonogestrel from the instant drug delivery system) and 20 (directed to the shelf life properties of the instant drug delivery system), the Office Action indicates that "[w]hile EP '815 does not disclose these properties, the drug delivery system rendered obvious by EP '815 is structurally identical to the instant drug delivery system (Office Action, page 7).

The Office Action further indicates that "[a]s a composition cannot be separated from its properties, and the drug delivery system rendered obvious by EP '815 is identical to the instant drug delivery system, the properties disclosed in instant claims 7 and 20 must be inherent in the drug delivery system of EP '815. This reasoning is supported by citing to Atlas Powder Co. for the premise that "[t]he discovery of a previously unappreciated property of a prior art composition, or a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." The Office Action also cites In re Best and MPEP §2112 for the premise that "the

claiming of a new use, new function, or unknown property which is inherently present in the prior art does not necessarily make the claim patentable" (Office Action page 7).

The Rejection of Claims 1-11, 13-16 and 20-21 Under 35 USC §103(a) Should be Withdrawn

Applicants respectfully traverse this rejection and submit that claims 1-11, 13-16 and 20-21 are not anticipated by EP'815.

Applicants' representative would like to direct the Examiner's attention to the fact that all references made in this response to text disclosed in the instant application refer to the paragraph of text in US2007/0141102 which represents the US Patent Application Publication of the instant application (serial number 10/594,104).

The outstanding obviousness rejection presently being applied to the instant application is premised on the same disclosure previously cited as the basis of an anticipation rejection under 35 USC §102 (EP 0876815, referred to herein as "EP '815"). All references made herein to the disclosure provided in EP '815 refer to the text of EP 0876815 A1 (referred to herein as EP '815A) publication by page and line number.

As indicated in the Response filed on December 21, 2009, the product Nuvaring®, represents a commercially available embodiment of the EP'815 DDS. The package insert for Nuvaring®, which has been made of record in the instant application, indicates on page 4, column 3, last paragraph entitled "Storage", that prior to dispensing to the user, Nuvaring® must be stored (at a temperature below room temperature) refrigerated 2-8°C.

> The Examiner has stated that "[a]lthough EP '815 discloses keeping the progestogenic steroid in a relatively low degree of **supersaturation** and further discloses that keeping the compound in low concentration improves the shelf life of the product, '815 *fails to teach the range "up to a concentration below the saturation level at 25° C as required by the instant claims*" (Office Action, page 6). In light of this statement, it is apparent that the DDS of the invention cannot be inherently present in the prior art. The instant invention is distinct from, and not obvious in view of the DDS disclosed in EP '815. The prior art device

required storage at a temperature below room temperature, the DDS disclosed and claimed in the instant application is physically stable when stored at or above room temperature.

As amended claims 1, 4 and 5 are directed to a DDS which requires the "progestogenic compound being dissolved in a core of a thermoplastic polyethylene vinylacetate copolymer **at** a concentration below the saturation level at 25°C." Accordingly, the amended claims define a range which is distinct from, and which does not overlap with, the range disclosed and claimed by the EP '815 patent.

In view of the Examiner's acknowledgement that EP '815 fails to teach the range encompassed by the limitation "at a concentration below the saturation level at 25° C" as required by the amended claims, Applicants respectfully submit that it is inconsistent to suggest that the instant disclosure represents an attempt to claim "a new use, new function or unknown property which is inherently present in the prior art." This assertion is based on the premise that the DDS disclosed and claimed in the instant application is distinct from the DDS embodied by EP '815 (based on the level of progestogenic steroid which is present in the devices and their physical stability at room temperature). Accordingly, the DDS of the invention is NOT present in the prior art DDS (exemplified by Nuvaring®) the patentability of which was at least partially based on the:

> "surprising finding that a steroid can be retained in a supersaturated state during prolonged storage (such as 6 months or longer) at temperatures between 4° C and 25° C, provided that the steroid concentration does not exceed the solubility at 25° C excessively (page 3, lines 12-15 of EP '815A).

Applicants would like to reiterate their position that EP '815 technically does NOT teach that keeping the compound dissolved *in a low concentration* improves the shelf life of Nuvaring®. Instead, EP'815 teaches a DDS wherein the progestogenic compound is dissolved in the core polymer in ***a relatively low degree of supersaturation***, and that it is the relative degree of supersaturation which makes a difference in the shelf life and efficacy of the EP'815 DDS as is illustrated on page 6, Reference Example and Table 2, which indicates that at a high degree of supersaturation no stable dosage form can be obtained.

Taking the saturation level of etonogestrel at 25°C in Evatane® 28-25 of 0.35%, it can be seen that all of the examples in EP'815 indicate that the relatively low degree of supersaturation means above one (Example 1 is 0.57/0.35=1.6; in Example 2, 0.75/0.35=2.1, and in Example 3 (Table 1) ranging from 0.57/0.35 to 0.75/0.35 which values are above one). None of the examples provided in EP'815 contain a saturation level of etonogestrel equal to one, let alone below one. Indeed, claim 5 (a preferred embodiment of EP'815), in setting forth a specific amount for a low degree of supersaturation, i.e., the amount dissolved is 2 to 5 times the amount necessary, further supports the proposition that some measure/degree of supersaturation of the progestogenic compound is required in the EP'815 DDS.

The instant specification indicates that the progestogenic compound (i.e., etonogestrel) in Nuvaring® is present at a concentration above the saturation level of etonogestrel at 25°C [see present specification Table I: Nuvaring® comparative, Evatane 28-25 (core material), etonogestrel at 0.69 wt% together with Table II: Material Evatane 28-25 (core material), saturation level of etonogestrel at 25°C being 0.35 wt%, 0.69/0.35=1.97]. The specification in paragraph [0100] further indicates that:

> [b]ecause of the concentrations above the saturation level at 25°C, etonogestrel in the samples of Nuvaring® and comparative example 1 may eventually crystallize out onto the skin of the device, which is undesirable.

In contrast, the improved DDS of the presently claimed invention is physically stable (meaning that the progestogenic compound *does not* crystallize onto the skin) under room temperature conditions, and thus does not require special storage and transportation conditions at a temperature below room temperature as is required for the EP'815 DDS (see paragraph [0023] of US2007/0141102). The improvement of being able to store the DDS of the presently claimed invention at 25°C prior to dispensing the DDS to the user, is attributed to having the concentration of etonogestrel at a concentration below the saturation level at 25°C. This is a distinct finding relative to the prior art discovery that "a steroid can be retained in a supersaturated state during prolonged storage (such as 6 months or longer) at temperatures *between 4° C and 25° C.*"

The instant specification explicitly states that having the progestogenic compound dissolved in the copolymer at a concentration below the saturation level at 25°C is an

essential feature of the invention. See for example paragraphs [0029], [0036] and description of the materials, concentrations and variables used to prepare the DDS of examples 1-14 as summarized in Tables I-III. The data provided in Table II of the instant specification provides the saturation level of etonogestrel (wt%) for nine different types of polyethylene vinylacetate copolymers at both 25° C and 37° C. A skilled artisan having access to the instant specification could easily discern the range of etonogestrel levels encompassed by the amended claims based on the particular type of copolymer selected for use as a core polymer. The information in Table III indicates that all but one (i.e., comparative #1) of the exemplified drug delivery systems of the invention are characterized by having the progestogenic compound concentration ***present at a concentration below saturation level at 25° C***.

Furthermore, because the efficacy of the EP '815 device is attributed to the devices ability to "release the active substances in a substantially constant ratio over a prolonged period of time" (page 2, lines 2-3 of EP '815A) which for contraception requires that:

> "the poly-EVA core body comprises etonogestrel and ethinyl estradiol in about a 1 to 0.2 – 0.4 ratio, more preferably in a 1 to 0.2 – 0.3 ratio by weight, whereby etonogestrel is dissolved in the poly-EVA material up to a relatively low degree of supersaturation . . ." (page 3, lines 49-51 of EP '815A), a skilled artisan would reasonably assume that modifying the level of the progestogenic from a level of supersaturation to a concentration below the saturation level at 25° C would alter the efficacy of the device.

It is further submitted that as amended claims 1, 4 and 5 are directed to a DDS which further recites the feature "…wherein the drug delivery system is physically stable when stored at or above room temperature" is patentable over EP '815 because EP '815 disclosure does not teach, suggest or motivate a skilled artisan to change the level of progestogenic steroid present in the DSS disclosed and claimed in EP '815 in order to achieve a DSS characterized by improved physical stability. More specifically, because the stability of the EP '815 device was attributed to the presence of the progestogenic steroid at a level of supersaturation it would not be reasonable to assume that a device characterized by the presence of a progestogenic steroid at a level below saturation at 25° C would even be stable at 4° C, let alone stable at 25° C.

For the reasons set forth above, Applicants are of the opinion that a skilled artisan would not modify the level of the progestogenic steroid present in the DDS disclosed in EP '815 in a manner which would lead to a DDS having a progestogen present at a concentration below its saturation level at 25° C. Reconsideration and withdrawal of the rejection of claims 1-11, 13-16 and 20-21 under 35 USC § 103(a), is requested.

CONCLUSION

Applicants believe that this paper addresses all issues raised in the Office Action. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (732) 594-5738.

It is believed that no fee is required for this submission. However, should any fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason, the Commissioner is authorized to deduct said fees from the Organon Deposit Account No. 50-4205 the appropriate large entity fee, referencing Attorney Docket No. 2004.834US.

Respectfully submitted,

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